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Abstract: Very low birth weight (VLBW) premature born infants have a high risk to develop visual perceptual and learning deficits as well as widespread functional and structural brain abnormalities during infancy and childhood. Whether and how prematurity alters neural specialization within visual neural networks is still unknown. We used functional and structural brain imaging to examine the visual semantic system of VLBW born (<1250 g, gestational age 25–32 weeks) adolescents (13–15 years, n=11, 3 males) and matched term born control participants (13–15 years, n=11, 3 males). Neurocognitive assessment revealed no group differences except for lower scores on an adaptive visuomotor integration test. All adolescents were scanned while viewing pictures of animals and tools and scrambled versions of these pictures. Both groups demonstrated animal and tool category related neural networks. Term born adolescents showed tool category related neural activity, i.e. tool pictures elicited more activity than animal pictures, in temporal and parietal brain areas. Animal category related activity was found in the occipital, temporal and frontal cortex. VLBW born adolescents showed reduced tool category related activity in the dorsal visual stream compared with controls, specifically the left anterior intraparietal sulcus, and enhanced animal category related activity in the left middle occipital gyrus and right lingual gyrus. Lower birth weight of VLBW adolescents correlated with larger thickness of the pericalcarine gyrus in the occipital cortex and smaller surface area of the superior temporal gyrus in the lateral temporal cortex. Moreover, larger thickness of the pericalcarine gyrus and smaller surface area of the superior temporal gyrus correlated with reduced tool category related activity in the parietal cortex. Together, our data suggest that very low birth weight predicts alterations of higher order visual semantic networks, particularly in the dorsal stream. The differences in neural specialization may be associated with aberrant cortical development of areas in the visual system that develop early in childhood.

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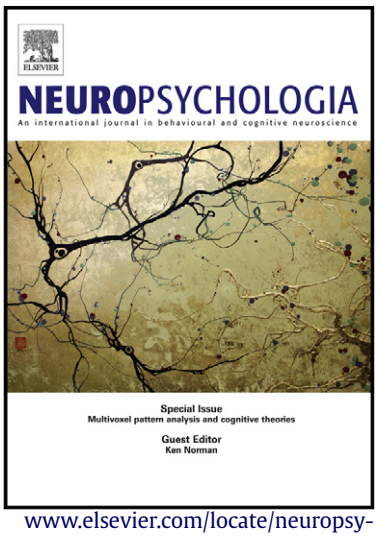

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Title:

Occipital cortical thickness in very low birth weight born adolescents predicts altered neural specialization of visual semantic category related neural networks.

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Abstract

Very low birth weight (VLBW) premature born infants have a high risk to develop visual perceptual and learning deficits as well as widespread functional and structural brain abnormalities during infancy and childhood. Whether and how prematurity alters neural specialization within visual neural networks is still unknown. We used functional and structural brain imaging to examine the visual semantic system of VLBW born (<1250 grams, gestational age 25-32 weeks) adolescents (13-15 years, n=11, 3 males) and matched term born control participants (13-15 years, n=11, 3 males). Neurocognitive assessment revealed no group differences except for lower scores on an adaptive visuomotor integration test. All adolescents were scanned while viewing pictures of animals and tools and scrambled versions of these pictures. Both groups demonstrated animal and tool category related neural networks. Term born adolescents showed tool category related neural activity, i.e. tool pictures elicited more activity than animal pictures, in temporal and parietal brain areas. Animal category related activity was found in the occipital, temporal and frontal cortex. VLBW born adolescents showed reduced tool category related activity in the dorsal visual stream compared with controls, specifically the left anterior intraparietal sulcus, and enhanced animal category related activity in the left middle occipital gyrus and right lingual gyrus. Lower birth weight of VLBW adolescents correlated with larger thickness of the pericalcarine gyrus in the occipital cortex and smaller surface area of the superior temporal gyrus in the lateral temporal cortex. Moreover, larger thickness of the pericalcarine gyrus and smaller surface area of the superior temporal gyrus correlated with reduced tool category related activity in the parietal cortex. Together, our data suggest that very low birth weight predicts alterations of higher order visual semantic networks, particularly in the dorsal stream. The differences in neural specialization may be associated with aberrant cortical development of areas in the visual system that develop early in childhood.

Keywords

prematurity; adolescents; semantic categories; visual development, visual memory

Learning about objects is a life long process that varies strongly between humans in both quality and quantity. The representation of objects in the brain has been associated with widely distributed neural networks. These networks characteristically reflect visual semantic categories such as "animals", "tools", "faces", or "landscapes" and likely represent structural perceptual object characteristics, as well as dynamical features and higher-order knowledge that relates to the object representation (Chao, Haxby, & Martin, 1999; Fairhall & Caramazza, 2013). The associated visual semantic neural networks seem to be established during early childhood, which then undergo further specialization until adolescence (Cantlon, Pinel, Dehaene, & Pelphrey, 2011; Peelen, Glaser, Vuilleumier, & Eliez, 2009). We have little information on how these networks develop and which factors determine the individual characteristics of visual semantic networks. One way to obtain information about early development of visual neural networks is by investigating children who are born prematurely. Neonates born prematurely or with a very low birth weight (VLBW) are at increased risk for later neurodevelopmental problems, neurosensory impairments, learning disabilities, behavioral and motor deficits (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Hack, 2006; Marlow, Wolke, Bracewell, & Samara, 2005). Abnormalities in grey and white matter structures have been suggested to relate to dysfunctional outcome in several behavioral and cognitive domains such as visual perception, motor skills, working memory, language, and hyperactivity (M. H. Beauchamp et al., 2008; Counsell et al., 2008; Ment, Peterson, Vohr, et al., 2006; Nosarti, Allin, Frangou, Rifkin, & Murray, 2005; Nosarti et al., 2008; Skranes et al., 2007). Interestingly, most of these brain structures develop much later than might be expected by the impact of brain injuries during the late gestation and perinatal period. It was therefore suggested that morphological and functional abnormalities might be caused by a cascade of events following premature birth, which may lead to reorganization of neural networks including brain areas that may have been spared at the time of premature birth (Bourne, 2010; Dammann & Leviton, 2006; Wattam-Bell et al., 2010).

We thus hypothesize that visual semantic category related neural networks are being reorganized after premature birth. The impact of prematurity on early visual development is relatively clear. For example, hemorrhage or hypoxia may injure the periventricular white matter and consequently impair early development of the primary visual sensory pathways and the development of the optical tract (Bassi et al., 2008; Cioni et al., 2000; Cioni et al., 1997). Such adverse events can lead to malformation of the visual sensory cortical areas (Martinussen et al., 2005; Zubiaurre-Elorza et al., 2012) and in severe cases may cause cortical blindness (Cioni et al., 1997). Whether and how early cerebral injury affects the maturation of visual functional neuroanatomy is yet unclear. Functional neuroanatomy of the visual system in preterm born children and adolescents has hardly

been investigated. Preterm born children, adolescents and adults have been shown to yield altered networks related to language (Ment, Peterson, Meltzer, et al., 2006; Mullen et al., 2011), response inhibition (Lawrence et al., 2009; Nosarti et al., 2006), and memory processing (Giménez et al., 2005; Narberhaus et al., 2009). Visual-cognitive neural networks in populations with developmental impairments other than those related to prematurity were associated with altered neural activity along the occipito-temporal and occipital-parietal pathways, i.e. in the ventral and dorsal visual streams. For example, impaired reading skills in children with developmental dyslexia were associated with reduced ventral visual stream tuning, meaning that dyslexics show less differentiated neural responses to words and word-like stimuli (van der Mark et al., 2009), while enhanced face processing related activity was found in the ventral visual stream of patients with Williams syndrome (Golarai et al., 2010). Reduced dorsal visual stream activity was associated with attention and working memory deficits in children and adults with ADHD (Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013) and in children with dyscalculia (Rotzer et al., 2009). Such findings are congruent with current view on neural development of the visual system. In that view dorsal and ventral visual streams follow different functional and neurodevelopmental trajectories (Klaver, Marcar, & Martin, 2011). White matter development of the dorsal visual stream seems to be characterized by strengthened inter-hemispheric connectivity, whereas alteration of regional cortico-cortical connectivity characterizes development of the ventral visual stream (Loenneker et al., 2011). Functional brain imaging studies revealed enhanced dorsal visual stream activity in adults compared to children related to motion defined visual perception as well as visuospatial memory and attention (Klaver et al., 2008; Klingberg, 2006; Lichtensteiger, Loenneker, Bucher, Martin, & Klaver, 2008). By contrast object recognition related activity in the ventral stream showed reduced activity related to unspecific object categories (Cantlon et al., 2011; Golarai et al., 2007; Klaver et al., 2008; Lichtensteiger et al., 2008; Passarotti, Smith, DeLano, & Huang, 2007; Peelen et al., 2009). It was suggested that neural tuning may increase neural specificity towards specialized object categories in the ventral stream (Grill-Spector, Golarai, & Gabrieli, 2008), whereas dorsal stream enhancement may reflect consolidation mediated specialization (Klaver et al., 2011). Hence, we would predict that VLBW adolescents show reduced neural activity in dorsal and enhance activity in the ventral visual streams. We also expect that structural changes of areas in the early visual system are associated with atypical neural activity in VLBW born adolescents.

To the best of our knowledge, the current study is the first to test these hypotheses by examining brain activity and morphology underlying high-order visual neural development in VLWB born adolescents. Together with term born control volunteers VLBW adolescents viewed animal and tool

pictures and scrambled versions of these pictures while brain activity was recorded with blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) scans. These visual categories are known to render activity in different "category-selective" neural networks in the dorsal and ventral stream of children and adults (M. S. Beauchamp, Lee, Haxby, & Martin, 2003; Chao et al., 1999; Dekker, Mareschal, Sereno, & Johnson, 2011). Specifically, perception of tool pictures elicits activity in visual-perceptual areas of the temporal lobe and visual-motor related areas in the intraparietal sulcus of the parietal lobe (Noppeney, Josephs, Kiebel, Friston, & Price, 2005; Vingerhoets, Acke, Vandemaele, & Achten, 2009). Perception of animal pictures elicits neural activity in temporal lobe areas related to visual-perception, and in some cases to biological motion related areas in the superior temporal sulcus (Allison, Puce, & McCarthy, 2000; M. S. Beauchamp et al., 2003). To investigate the effect of very low birth weight on neural networks underlying visual semantic categories, we tested VLBW adolescents who were born between 1992 and 1994 with a birth weight <1250 gram. We hypothesized that VLBW participants would yield specific visual deficits accompanying deviant brain activity compared to term born matched control adolescents. In addition we measured cortical thickness and surface areas of brain structures related to the visual system because these morphological changes have been associated with cognitive functioning in VLBW adolescents (Bjuland, Løhaugen, Martinussen, & Skranes, 2013; Skranes et al., 2013). We correlated these brain morphometric measures with category related brain activity in each group and with perinatal factors (birth weight/gestation age) in VLBW adolescents. We expected that lower birth weight relates to morphometric abnormalities in the early visual system in VLBW adolescents and that these abnormalities would be associated with atypical category related brain activity.

Methods

Participants

Eleven VLBW born adolescents (mean age 14.7 years, range 13.8-15.3, 4 male) and eleven term born (TB) adolescents (mean age 13.3 years, range 12.1-14.1, 4 male) were scanned. All VLBW adolescents were part of a longitudinal cohort of children born between 1992 and 1994 with a birth weight < 1250 g (M = 951 g, SD = 145) and a gestational age between 25.7 and 31.7 weeks (M = 28.7 weeks, SD = 2.1). They were recruited in the neonatal period and followed prospectively until adolescence. Repeated neurodevelopmental assessments were performed at three, nine and 24 months corrected age and at six and ten years (Latal-Hajnal, von Siebenthal, Kovari, Bucher, & Largo, 2003; Natalucci et al., 2013; Schmidhauser et al., 2006; Seitz et al., 2006). Mean birth weight of this sample was slightly lower than in the larger samples tested at age ten, whereas gestation age was comparable, 1008 g and 28.6 weeks in Natalucci et al. (2013). Children with

major neurodevelopmental and neurosensory deficits such as cerebral palsy, severe hearing or vision impairment or mental retardation or with neonatal cerebral ultrasound abnormalities (> grade 2 intraventricular hemorrhage or cystic periventricular leukomalacia) were excluded. Term born adolescents were recruited by asking the VLBW adolescents to bring their best friends to facilitate matching for socioeconomic background, sex, age, and general intelligence. Additional TB adolescents were recruited in the region Zurich. VLBW and TB adolescents were matched for IQ, gender, and socio-economic background (Table 1). Socio-economic status was evaluated by means of a 6-point scale of paternal occupation and maternal education ranging from 2 to 12 (Largo et al., 1989). All participants were right handed (Edinburgh handedness inventory), had no history of neurological or psychiatric disorder. Visual acuity was normal or corrected during scanning. Age was not matched, as the VLBW adolescents were about one year older (14.8 vs. 13.3 years, Table 1). Since we encouraged VLBW adolescents to ask their best friends to participate in the study, this strategy may have caused that their friends were younger and matched school class or general level of performance. One additional TB adolescent was excluded from the analysis due to technical problems at scanning and one additional VLBW adolescent was excluded because not all neuropsychological tests were completed. All participants and parents of the adolescents gave written informed consent prior to participation and all participants volunteered in other imaging protocols that will be reported elsewhere. They were given movie or book vouchers as a token of our appreciation and participated in a lottery that was drawn at the end of the study in which they could win an I-pod. The study was approved by the local ethics committee at the University Children‘s Hospital.

General procedure

All participants came on two separate days. On one day, functional and structural scans were acquired as well as a set of neuropsychological tests for visual perception, visuomotor integration and motor coordination. These tests included Beery-Buktenica Developmental Test of visual motor integration (VMI), and control tasks for visual perception (VP) and motor coordination (MC) (Beery, Buktenica, & Beery, 2004), visual organization task (VOT) (Hooper, 1983), and mental rotation (LPS7) (Horn, 1983). In addition, to control for general knowledge on animals and tools, a series of pictures of 60 animals and 60 tools were given to them on paper after scanning. Pictures were named and rated for familiarity by asking for all pictures: “what is the name of this picture”, for animal pictures “how often did you see this animal” and for tool pictures “how often did you use this tool”. They wrote down the names of the animals or tools on the questionnaire and rated the last two questions on a Likert scale from 1 to 9. The full questionnaire could be filled in at home and participants were encouraged to perform this task without help. On another day, participants

underwent testing for general intelligence (German version of the Wechsler Intelligence Scale for Children- IV (Petermann & Petermann, 2003), motor performance (Zurich Neuromotor Assessment, ZNA) (Largo, Caflisch, Hug, Muggli, Molnar, & Molinari, 2001; Largo, Caflisch, Hug, Muggli, Molnar, Molinari, et al., 2001) and visual acuity (Bailey & Lovie, 1976). The order of examination days was balanced across participants.

fMRI task description

Subjects viewed colored pictures of animals and tools in the scanner. The pictures were selected from a commercial picture database (http://www.hemera.com/). Scrambled versions of these pictures as control stimuli. For this purpose each picture was Fourier transformed into their distributions of r/g/b colors using a custom Matlab script. Then, frequencies of each color were randomly re-ordered in plane so that all frequency and color information maintained in the control stimuli. All stimuli were presented on a grey background during 800 ms followed by a 200 ms inter-stimulus interval. Stimuli were presented in blocks of 10 trials (10 seconds) that were separated by a 16 second interval. All conditions were presented in a balanced order of eight blocks of trials (2 blocks per condition). Two versions were created with a different order of blocks that were balanced across subjects. During inter-stimulus intervals a white fixation cross was shown. Stimuli were presented through optical goggles. The experiment lasted for about 4 minutes. It started with an instruction (4 seconds) and fixation period (7 seconds), followed by stimulus presentation (3 minutes and 28 seconds) and ended with a fixation cross until scanning was completed. All participants were instructed to passively view the visual stimulation.

Data acquisition

Brain images were acquired on a 3.0 T Scanner (General Electric, Milwaukee USA) using a standard 8-channel head coil. To estimate blood oxygenation level dependent (BOLD) contrast 124 echo planar imaging (EPI) scans were acquired preceded by 3 dummy scans. The scans were tilted 15° after alignment to the AC/PC axis to reduce susceptibility artifacts near inferior temporal regions (Weiskopf, Hutton, Josephs, & Deichmann, 2006). Scan parameter were: number of slices (NS): 35; slice thickness (ST): 3 mm; matrix size (MS): 64×64; field of view (FOV): 200 mm; flip angle (FA): 75°; echo time (TE): 32 ms; repetition time (TR): 1.9 s. The task was presented via video goggles (MRI Audio/Video System, Resonance Technology, Inc., USA) using Presentation software (www.neurobs.com). Additionally, a high-resolution anatomical reference T1-weighted scan was acquired to test for abnormalities in brain anatomy and for morphometric analysis (NS: 140; ST: 1.2 mm; MS: 512×512; FOV: 240 mm; FA: 13°; TE: 4.5 ms; TR: 10.9 s). All participants further participated in additional scanning sessions that will not be reported here.

Data analysis

Neuropsychological test scores were compared between groups after correction for age using multivariate analysis of variance when normal distribution could be assumed (based on Shapiro-Wilk test results). Mann-Whitney U tests was used for variables with a non-normal distribution implemented in SPSS 21.0. Data are considered to be significant at $p < .05$.

All T1 brain anatomical images were anatomically evaluated for malformations, tissue proliferation, signal intensity changes, or volume loss by an experienced neuroradiologist who was blinded for patient characteristics (EM). No major MR abnormalities were observed so that all images were included in further analyses. Images were transformed into analyze format and fed into a standard morphometric analysis using Freesurfer version 4.5.0 for Linux (http://surfer.nmr.mgh.harvard.edu) (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). This software separately calculates volumes for global brain and subcortical structures, as well as volume, thickness and surface area of cortical regions in each hemisphere. The cortical stream tesselates each hemisphere on the grey-white border and allows for the measurement of cortical thickness at each point of the tesselation. In addition, the volume, surface area and cortical thickness of individual gyri and sulci can be measured. We restricted our analysis to cortical thickness and surface area of occipital, parietal, ventral and lateral temporal regions (Desikan et al., 2006). Further, in order to be able to better compare our morphometric data of the VLBW group with larger samples from other studies, we additionally measured total brain volume, volumes of the cerebral cortex and white matter, cerebellum cortex and white matter. Cortical thickness and surface area were pooled over the left and right hemispheres. Freesurfer statistics were then evaluated with SPSS 21.0. Due to the known negative correlation between age and gray matter volumes and the expected difference in total brain volume between VLBW and term born controls we compared groups with total brain volume and age at scan as covariates, except for measures with a non-normal distribution that were compared using Mann-Whitney U tests.

Functional MRI data analysis was done using Statistical Parametric Mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included realignment with unwarping. No subject was excluded from the analysis because of excessive movement. Exclusion criteria were movements exceeding 2.0 mm and 0.6 degrees in any direction, which was less than 1 voxel size. Functional and anatomical data were transferred into a common stereotactic space by estimating normalization parameters for functional MRI images on standard (EPI and T1) templates in Montreal Normalization Institute space. Normalization parameters were applied to resample both

the EPI images (3 mm^3) and T1 images (1 mm^3). EPI data were then smoothed with a 9 mm full width at half maximum isotropic Gaussian kernel to be able to accommodate for larger variability between groups. The hemodynamic response was modeled by a stick function to each stimulus presentation in each category convolved with a canonical hemodynamic response function and its temporal derivative. Parameters were generated for four categories: animal pictures, tool pictures and scrambled versions of these pictures. To determine category related regions of interest, voxels were interrogated on two subsequent questions. Voxels were first tested at the group level to respond to pictures more than scrambled images across all participants ($p < .001$). Voxel were then tested to be differently responsive to animal and tool pictures (uncorrected $p < .05$, cluster size > 10 voxels) (Chao, Weisberg, & Martin, 2002). The local maxima were defined and classified by the SPM anatomy toolbox (v1.8) (Eickhoff et al., 2005). ROIs were created as 6 mm spheres around local maxima of tool and animal category related areas across all subjects using MarsBar toolbox (http://marsbar.sourceforge.net/). For the case of data reduction the ROIs had to lie at least 16 mm apart. Mean percentage signal change for each condition was extracted from unsmoothed data of each subject. These values were submitted to a repeated measures analysis of variance with age at scan as covariate. Category and group differences, as well as interactions between group and category were tested using SPSS 21.0 and considered to be significant at a threshold of $p < .05$.

Multiple regression analyses were applied to test the relationship between brain structure in the visual system and semantic category related activity in each group separately. Here we used the cortical thickness and surface area of the same cortical regions as described above as anatomical predictors. Results for global brain volumes were not reported. Semantic category related activity was determined in ROIs selective to animals (animal > tool picture) and tools (tool > animal picture) as described above. Age at scan and total brain volume were initial predictors in the model. Morphometric data were predictors in the second step of the regression model to test if cortical structures explain additional variance. Regression coefficients were compared between groups using Z-transformed partial coefficient comparisons (Cohen, Cohen, West, & Aiken, 2003). To test whether birth weight and gestational age predicted morphological variability within the visual system of VLBW adolescents we applied multiple regression analyses with total brain volume, age at scan as initial predictors and gestational age and birth weight as predictors in the second step of the regression model.

Results

Cognitive, visual and motor performance

Table 1 shows the test scores and group comparisons. VLBW adolescents were about one year older than the TB adolescents. Therefore, groups were compared with age as covariate whenever a normal distribution could be assumed. No difference between groups was found in estimated overall IQ, visual organization performance, Beery visual perception, motor coordination and visuomotor integration task (all $p > .05$). Two VLBW adolescents scored below the norm on the Beery visual perception task, two other VLBW adolescents scored below the norm on both the Beery motor coordination and visuomotor integration task, and one VLBW adolescent on the motor coordination task only. No control participant scored below the norm. Visual acuity and mental rotation performance (LPS7) was significantly lower for VLBW adolescents as compared with controls. Visual acuity was normal in most participants (Snellen-Index > 0.3) except for one VLBW adolescent with an uncorrected visual acuity of 0.15 and one with a visual acuity of 0.3. Neuromotor skills were comparable between groups, except for the adaptive fine motor task. Here VLBW adolescents yielded significantly lower performance levels than TB adolescents ($p = .044$). To provide an indication of the representativeness of our sample we compared the ZNA scores with the larger longitudinal cohort of VLBW children tested at age ten years (n=65) from which this sample was selected (Natalucci et al., 2013). Our subsample can be compared to that study since in that analysis children with cerebral palsy and mental retardation were also excluded. Median ZNA scores of our current sample were within the range of those for the larger sample: pure motor median z-score in our sample (range in Natalucci et al. 2013)) = 0.5 (-4.9/3.9), static balance 0.1 (-4.7/2.3), adaptive fine motor -0.2 (-3.5/3.4), adaptive gross motor -0.8 (-3.8/2.0).

Naming and familiarity of animal and tool categories

Three VLBW participants did not return the questionnaire for naming and familiarity rating of the animal and tool pictures. After excluding these participants the analysis revealed that animal pictures were named more often correctly than tool pictures (tools 80 %, animals 93 %; $t_{18} = 4.9$, $p < .001$). There was no significant difference between groups. Rating results on a 9-point Likert scale showed no familiarity difference in the use of tools and of viewing animals (tools 5.2, animals 4.9, $p > .3$). There was no significant difference between groups on this task.

Neural activity in visual category related networks

Tools > animal pictures: Visual category related activity in each group is illustrated in Figure 1. Inspection of that figure yields visual category related neural networks in both TB and VLBW born adolescents. TB adolescents show typical enhanced neural activity elicited by tool pictures as compared to animal pictures in dorsal and ventral visual brain areas. VLBW born adolescents seemed to show a smaller neural network selectively responding to tool pictures. The statistical

analysis of the ROI data (ANOVA with group as between-subject and category as within-subject factor) revealed a significant main effect of category (tool > animal pictures) in the bilateral fusiform gyrus and left inferior temporal gyrus (Table 2, Figure 2). Dorsal visual stream activity was found in the bilateral superior parietal lobule and left anterior dorsal part of the supramarginal gyrus (area PFt). No main effect of group was found, but a significant interaction between category and group indicated group differences in tool picture related brain activity in the left area PFt (p = .033) (see Figure 2 and Table 2 for details). Here, only TB adolescents yielded enhanced neural activity for tool compared to animal pictures (p < .001). Due to the small group size, the results of the ANOVA with age as covariate might be inaccurate and lead to false positive results. We therefore first tested and found that normal distributions could be assumed for the category related ROI data (tools vs. animal pictures) in area PFt. Secondly, Mann-Whitney tests confirmed the group differences on the category related activity in area PFt (U = 14, p = .002).

Animals > tool pictures: Inspection of figure 1 suggests typically enhanced activity for animal pictures compared to tool pictures in several areas in occipital cortex and fusiform gyrus of TB adolescents. VLBW born adolescents seem to yield activity in a more extensive network related to perception of animal pictures including occipital areas and areas further up into the ventral stream, as well as in the medial temporal lobe. The ROI analysis showed a significant main effect of category (animal > tool pictures) in the bilateral cuneus and middle occipital gyrus, right middle temporal gyrus, right fusiform and lingual gyrus, right precentral gyrus and left middle frontal gyrus (Figure 2, Table 2). A significant group effect was found in the right lingual gyrus, left middle occipital gyrus, cuneus and middle frontal gyrus where VLBW adolescents showed enhanced neural activity to pictures as compared with TB controls. A significant group by category interaction was found in the left middle occipital gyrus and right lingual gyrus. Only VLBW adolescents elicited enhanced animal as compared with tool category related activity in these areas (respectively p = .009 and p = .002). Due to the small group size the results of the ANOVA with age as covariate might be inaccurate. We therefore tested and found that normal distributions could be assumed for category related ROI data (animal vs. tool pictures) in regions that showed interactions between group and category related activity. Mann-Whitney tests confirmed the group differences on the category related activity in the left middle occipital gyrus (U = 20, p = .008) and right lingual gyrus (U = 25, p = .020). All ROIs that showed a main effect of group were normally distributed for unspecific picture related activity, except for the left middle occipital gyrus. Only the left middle occipital gyrus and left middle frontal gyrus showed significant group differences on the non-parametric tests (U = 27, p = .028 and U = 25, p = .020). Negative correlations between age and picture related activity in VLBW for the right lingual gyrus (Spearman rho = -.70, p = .016) and in

TB for the left cuneus (Spearman rho = -.76, p = .006) might have confined the difference between groups. Hence, group differences on category related activity in the right lingual gyrus and left middle occipital gyrus and on picture related activity in the left middle occipital gyrus and middle frontal gyrus could reliably be related to group difference in birth weight. By contrast, unspecific picture related activity in the right lingual gyrus and left cuneus might be attributed to age rather than birth weight differences between groups.

Morphometry

The parietal cortex was significantly thinner as compared to term born adolescents, whereas the cortical surface area was of similar size. Although all subregions of the parietal cortical regions tended to have reduced thickness, only the superior parietal gyrus, inferior parietal gyrus and the precuneus were significantly thinner in VLBW adolescents (see Table 3 and supplementary Table 1 for details). Groups did not significantly differ in cortical thickness or surface area of the occipital, ventral and lateral temporal cortices. Total brain volume, cerebral grey and white matter as well as cerebellar grey and white matter did not significantly differ between groups.

Associations between morphometry and category related neural activity

The relationship between morphometry of the visual system and category related brain activity was evaluated separately in each group and subsequently compared between groups. We focused on the category related group differences within left area PFt, the right lingual gyrus and left middle occipital gyrus. However, since we found no significant relationship between category related brain activity in the left middle occipital gyrus and cortical thickness or surface area of any region in the visual system, we provide no details on those results.

Left area PFt: In VLBW born adolescents tool > animal category related activity in area PFt correlated negatively with the cortical thickness of the occipital cortex and positively with the surface area of the lateral temporal cortex (Table 4). The negative association with the cortical thickness of the occipital cortex was not found in term born controls but partial correlation coefficients not significantly differ between groups. Detailed inspection of the cortical thickness of substructures in the occipital cortex revealed that only the cortical thickness of the pericalcarine gyrus was significantly associated with brain activity in VLBW adolescents and partial correlation coefficients differed between groups (p = .001, see Figure 3 and supplementary table 2 for details). The positive association between tool category related activity and surface area of the lateral temporal cortex was found in VLBW adolescents, but not in TB adolescents. However, partial correlation coefficients did not significantly differ between groups. Detailed inspection of surface

areas in subregions of the lateral temporal cortex showed a positive association between surface area of the superior temporal gyrus and tool related activity in VLBW adolescents. Group differences on partial correlation coefficients revealed a trend to significance for that area (p = .068). In sum, the data suggest that thicker pericalcarine cortex and to some extent smaller surface area of the superior temporal gyrus in VLBW adolescents were associated with reduced tool related activity in the parietal cortex.

Right lingual gyrus: We examined the relationship between morphometry and animal category related activity within the right lingual gyrus. The regression analysis showed that animal > tool picture related activity in the right lingual gyrus of VLBW adolescents was not significantly associated with cortical thickness or surface area of any region of interest (Table 4). Term born controls showed a positive correlation between animal category related activity in the right lingual gyrus and surface area of the lateral temporal cortex. VLBW adolescents did not show this relationship and correlation coefficients significantly differed between groups (surface area p = .006). Detailed inspection of surface areas in subregions of the lateral temporal cortex yielded a significant positive association between activity and surface areas of the bank of the superior temporal sulcus and the middle temporal gyrus. Partial correlation coefficients significantly differed between groups for the association between animal category related activity and surface area of the bank of the superior temporal sulcus (p = .01, Figure 3, supplementary table 2). Hence, enhanced animal category related activity could not be clearly associated with morphometric measures in VLBW, whereas surface area of bank of the superior temporal sulcus in the lateral temporal cortex was positively associated with animal category related activity in the right lingual gyrus of term born adolescents.

Associations between morphometry and perinatal factors

Age and total brain volume significantly explained variance for surface area, but not cortical thickness of all regions of interest. Birth weight and gestational age explained additional variance for the cortical thickness of the occipital cortex and surface area of the lateral temporal cortex (Table 5). Higher birth weight was associated with reduced cortical thickness in the occipital cortex (β = -.712, p = .037), and increased surface area in the lateral temporal cortex (β = .342, p = .027). To determine whether specific cortical regions could be identified as being sensitive to birth weight, we replaced the second step in the model by specific subregions (supplementary Table 3). We found that higher birth weight significantly associated with thinner cortex of the pericalcarine gyrus (β = -.745, p = .014, Figure 4). Birth weight was also associated with larger surface area of the

superior temporal gyrus (β = .409, p = .016). Gestational age did not significantly explain cortical thickness or surface area of any region of interest.

Discussion

This study investigated the question whether very low birth weight born adolescents show deviations in visual semantic category related brain activity and whether these deviations could be related to differences in brain morphology of the early developing visual system. We found evidence that tool category related activity in the dorsal visual stream was attenuated and that animal category related activity in the ventral stream was enhanced in VLBW adolescents. Further results showed that birth weight predicted alterations in morphology of the occipital cortex and lateral temporal cortex of VLBW adolescents, whereas these morphological alterations could partly explain reduced tool category related activity in the dorsal visual stream. This and other evidence illustrate the impact of premature birth on the maturation of structural neuroanatomy and specific functional networks of the visual system.

Atypical visual category related brain activity in VLBW adolescents

Our first question was whether category related activity differed between VLBW and term born adolescents. In line with our expectation we found reduced tool related activity in the dorsal stream of VLBW adolescents. Tool related activity in the ventral stream, however, did not differ between groups. We also found that all pictures, and particularly animal pictures elicited enhanced activity in the ventral part of the posterior ventral visual stream of VLBW adolescents, but also in the middle frontal gyrus. These findings support the hypothesis that VLBW adolescents yielded atypical neural development of the visual system. In line with the dorsal vulnerability hypothesis (Atkinson & Braddick, 2007; Braddick, Atkinson, & Wattam-Bell, 2003), we found indications of impaired development of the dorsal stream. However, in line with our more general hypothesis, the enhanced activity in the ventral stream suggests that activity in both pathways are changed and that impairment is expressed as hypoactivity in the dorsal and hyperactivity in the ventral visual stream.

The findings are in line with studies on atypical development that showed reduced parietal activity in patients with ADHD or dyscalculia (Cortese et al., 2012; Hart et al., 2013; Rotzer et al., 2009) and hyperactivity in the ventral stream of patients with Williams-syndrome or in preterm born adolescents during a no-go task (Golarai et al., 2010; Nosarti et al., 2006). Since activity in area PFt links to imagery and planning of grasping and visuomotor integration (Noppeney et al., 2005; Vingerhoets et al., 2009), we suggest that reduced PFt activity is associated with impaired visuomotor imagery abilities in VLBW adolescents. This is in line with our finding that

neuropsychological outcome in our sample and in a larger comparable cohort at age six and ten yielded impaired visuomotor integration functions (Natalucci et al., 2013). The pattern of atypical activity in VLBW adolescents cannot be explained by the age difference between VLBW and term born adolescents. On the contrary, the older VLBW group shows a pattern that partly resembles a pattern one might expect of a younger group (Klaver et al., 2011). Children typically show reduced activity in the dorsal visual stream compared to adults for visual motion perception and attention/working memory related tasks (Klaver et al., 2008; Klingberg, 2006; Lichtensteiger et al., 2008), while they show enhanced unspecific posterior ventral activity and reduced specific anterior ventral activity that might be associated with underdeveloped visual category specialization and neural tuning (Cantlon et al., 2011; Peelen et al., 2009). Our findings are interesting in comparison with a study that investigated typical neural development of visual semantic networks for animal and tool pictures (Dekker et al., 2011). The authors examined six to ten year old children and young adults during a passive viewing task. They used a similar task and the reported networks were comparable with the term born controls in our study. They found no global network difference between age groups but reported a negative relationship between age and object induced activity in the medial parts of the fusiform gyrus (ventral visual stream) within the group of children. Our VLBW adolescents sample was on average one year older than the TB controls and about six years older than the sample by Dekker and colleagues. A developmental lag hypothesis would predict a large six-year delay, which is not in line with the cognitive and behavioral data in our sample and with the atypical pattern of category related neural activity. Hence, functional reorganization during development, rather than delayed development is likely to be associated with the atypical visual category related activity in VLBW adolescents.

Structure and function relationships in VLBW adolescents

Our second question was whether morphological abnormalities in the early visual areas are associated with atypical neural activity in higher order visual areas. This hypothesis could partly be confirmed. We found that dorsal visual stream activity was associated with thicker occipital cortex, particularly in the pericalcarine gyrus of VLBW adolescents. Smaller surface area of the lateral temporal cortex, specifically in the superior temporal gyrus was also associated with reduced activity in that group. Furthermore, lower birth weight was associated with increased cortical thickness of the occipital cortex, including the pericalcarine gyrus, and reduced surface area of the lateral temporal cortex, specifically the superior temporal gyrus. This further supports the idea that the association between reduced tool related parietal activity and cortical development of the occipital and lateral temporal cortex is mediated by lower birth weight. Hence, we suggest that perinatal events caused changes in occipital cortical thickness and lateral temporal cortical surface

area, which impaired building of connections with distant areas of the dorsal visual system. The visual sensory input of tool pictures in the primary visual cortex may thus not be accurately transferred to specialized areas in the dorsal stream of VLBW adolescents.

This idea is supported by anatomical connectivity, developmental neuroscience and neuroimaging studies. Anatomical connectivity studies distinguished dorsal and ventral sections within the dorsal visual stream and showed direct dorsal connections between the pericalcarine cortex and the superior parietal lobe (medial intraparietal area) and indirect ventral connections to the lateral inferior parietal lobe via the lateral temporal cortex (Rizzolatti & Matelli, 2003). Area PFt is located in the anterior part of the inferior on the border of the intraparietal sulcus, close to somatosensory area 2 (Caspers et al., 2006; Eickhoff et al., 2007). The area may thus mainly receive indirect input from the visual cortex via area MT and the superior temporal polysensory area. Interestingly we also found that tool picture related brain activity correlated positively with cortical surface area of the lateral temporal cortex in VLBW. The superior temporal gyrus is not directly connected to the pericalcarine gyrus, but both are connected to the lateral occipital gyrus (Human Connectome Project, Joshi et al. (2010), http://www.humanconnectomeproject.org). This suggests that tool related activity in area PFt of VLBW adolescents relies on both cortical thickness of early visual areas and intermediating structures in the ventral part of the dorsal stream (superior temporal gyrus). In concordance with the anatomical connectivity data and the fact that connections between area V1 and surrounding areas in the visual cortex develop during infancy (e.g. Johnson 1990) one might speculate that development of the lateral temporal cortex at least partially depends on structural integrity of the early visual cortical areas.

We found no clear relationship between early visual structures and category related activity in the ventral visual stream in VLBW adolescents. However, animal category related activity in the right lingual gyrus was associated with the surface area of the lateral temporal cortex, particularly the bank of the superior temporal sulcus in term born adolescents. We can think of two neurodevelopmental mechanisms that might contribute to this finding. First, neural tuning in the ventral stream of term born adolescents may depend on advanced organization of specialized areas in the lateral temporal cortex. The superior temporal sulcus is known to be associated to functional specialization of biological motion (Allison et al., 2000). Specialized activity in this region is not completed before school age, while immature activity is also associated with enhanced activity in the fusiform gyrus (Lichtensteiger et al., 2008). One might thus suggest that neural tuning in the ventral visual stream and structural maturation of the lateral temporal cortex are associated, which also in line with recent hypotheses on functional and structural abnormalities in dyslexia (Richlan,

Kronbichler, & Wimmer, 2013). Second, top-down processes might explain differences between VLBW and term born adolescents. Nosarti and colleagues found that enhanced posterior ventral activity and prefrontal activity accompany processing of attention demanding distractors and no-go stimuli during a go-no-go task (Nosarti et al., 2006). We also found enhanced left frontal activity in VLBW adolescents, while specialization in the ventral stream of term born adolescents could be related to structural integrity of the bank of the superior temporal sulcus. Hence, we suspect that enhanced activity in the ventral stream may relate to compensatory processes reflected in a ventral occipito-frontal hyperconnectivity. At the current stage, these explanations remain rather speculative and are open for further investigation.

Possible mechanisms for structure and function relationships in VLBW adolescents

Several studies reported that alterations in cortical thickness and reductions of cortical surface area relate to cognitive impairments in VLBW adolescents (Bjuland et al., 2013; Skranes et al., 2013) and in other populations with developmental disorders (Meda, Pryweller, & Thornton-Wells, 2012; Von Rhein et al., 2014). Although we still know very little about structure and function relationships it is likely that changes in cortical thickness and surface area have different causes and also differently predict brain activity.

Cortical thickness is thought to depend on the process of grey matter dendritic arborization and pruning and the degree of myelinization at the gray/white matter border (Huttenlocher, 1990; Sowell et al., 2004). In many regions cortical thinning or cortical thickening is related to maturation and changes in cortical thickness have also been associated with maturation of brain activity (Lu et al., 2009; Nuñez et al., 2011). Abnormal cortical thickness has also been associated with deviant brain activity in patients (Foland et al., 2008; Rasser et al., 2005). One possible explanation for abnormal cortical thickness in VLBW adolescents is that antenatal intrauterine infections, fetal inflammatory response and oxygen supplementation affects the retina and visual brain pathways (Dammann & Leviton, 2006; Sears, Pietz, Sonnie, Dolcini, & Hoppe, 2009). Such adverse events can destruct ascending and descending axons, which may deprive visual input and isolate output and in turn leads to blunted neural differentiation in grey matter (Inder, Warfield, Wang, Hüppi, & Volpe, 2005). Alternatively, variations in oxygen supplement may affect cortical vascular development, which in turn might be linked to synaptogenesis requirements that proceed differently for the magno- and parvocellular systems in the primate cortex (Fonta & Imbert, 2002). In that process early visual exposure may also contribute to the early vascular and neural development of the visual system (Bengoetxea, Argandoña, & Lafuente, 2008). Considering the lack of white matter injuries on the occipital tract in our sample and the dissociation in synaptogenesis

requirements for the dorsal and ventral stream we suppose that the vascular hypothesis is more plausible. We thus suggest that connections between the pericalcarine gyrus and the ventral part of the dorsal stream are disrupted in VLBW adolescents, which may lead to aberrant connectivity and impaired transfer of tool picture related neural signals to specialized neurons in PFt. However, we clearly do not have sufficient clinical information about the perinatal period of our sample to make retrospective inferences on the causes of abnormal visual development.

Studies that related surface area to brain activity are rare. However, increase in grey matter volume has been associated with functional plasticity and expertise in both patients (Golarai et al., 2010) and healthy controls (Hänggi, Brütsch, Siegel, & Jäncke; Maguire et al., 2000). It is known that white matter injuries due to intraventricular hemorrhage or periventricular leukomalacia can have impact on the development of cortical columns and grey matter volume. IVH can disrupt the pool of progenitor cells that migrate to the cortex and build cortical columns, while PVL has been associated with a so-called dying-back mechanism, a loss of neuronal somata after axonal disruption, which indirectly affects cortical development (Volpe, 2009). Although no VLBW adolescent had an IVH or PVL diagnosis, diffuse white matter injury may still affect cortical development along similar dying-back mechanisms associated with PVL. Skranes et al. (2013) explained reduced surface area of the superior temporal gyrus in VLBW adolescents to be associated with diffuse white matter injury of long association fiber tracks. That region has also connected more to the dorsal stream of adults than in children by fiber connections crossing the splenium of the corpus callosum (Loenneker et al., 2011). All these tracks are at risk for reduced fractional anisotropy in VLBW adolescents (Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011; Skranes et al., 2007), suggesting that subtle white matter injuries in these tracks have indirect effect on cortical maturation. Hence, we postulate that very low birth weight is associated with the vulnerability of structural connectivity with the lateral temporal cortex. Deficient structural connectivity via long association fibers and with early visual cortical areas might then have negative impact on late cortical development of the lateral temporal cortex, which then impairs functional specialization of higher order visual processes in the dorsal and ventral visual stream.

Methodological considerations

Several limitations need to be accounted for in this study. First, our sample size was small, yielding the possibility of a selection bias, a lack of statistical power and inhomogeneity of the data. We suggest that at least neuropsychological and morphological test statistics might be underestimated, whereas we could minimize the chance for false positive results. Our study sample was a subgroup of eighteen VLBW adolescents and sixteen controls. Twelve participants were randomly assigned

to this fMRI study, while two participants needed to be excluded because of technical problems. All participants received the neuropsychological testing and anatomical scanning, so that we could validate at least the neuropsychological outcome and structural data between two groups. That extended group analysis confirmed our report on the neuropsychological outcome and structural data comparison between VLBW and TB control adolescents (data not shown). Since our sample was a subset of a larger longitudinal cohort, we could also compare our data on motor functions and visuomotor integration as measured with the ZNA test battery in VLBW children at age six and ten. Our small sample scored comparable with the full sample of VLBW children examined at ten years of age (Natalucci et al., 2013). Although ZNA fine adaptive motor scores were still significantly reduced in our smaller sample of VLBW adolescents the results of the neuropsychological testing may underestimate true characteristics of VLBW adolescents due to a lack of statistical power. Our morphometric data also match earlier findings for premature born children and adolescents with very low birth weight, yielding comparable values for grey and white matter volumes in VLBW and term born adolescents (cf. Bjuland, Rimol, Løhaugen, and Skranes (in press); Martinussen et al. (2009); Taylor et al. (2011)). Since those studies reported significant group differences in several brain grey/white matter volumes, our limited statistical power may underestimate the true morphological differences between VLBW and term born adolescents. Functional fMRI data were highly compatible with previous reports on animal and tool related activity in term born children and adults (Dekker et al., 2011). We evaluated fMRI data using SPM8, which employs a parametric approach that uses the General Linear Model to generate statistics at every voxel in the brain. This model assumes that the data are obtained from stationary homogeneous discrete Gaussian fields. If intra-individual variability in the BOLD signal is large it is difficult to know if the data in each voxel are normally distributed. We could alternatively have analyzed the data with a permutation-based approach, which is not often used, but may perform better in small groups where the assumptions of parametric analyses are hard to test (Nichols & Holmes, 2001). We used ROI analyses to compare groups and tested whether the assumptions of homogeneity of variance and normality of distributions were violated. Functional and structural data were in large parts normally distributed and showed similar distributions between groups. Nevertheless we also tested and confirmed our main findings using non-parametric analyses. It also needs to be noted that our subject sample of VLBW adolescents were all normally performing adolescents with normal IQ. This may be a positive selection bias for the whole population of VLBW adolescents that were often reported to have lower IQ, e.g. Bhutta et al. (2002). Many VLBW who were originally prospectively recruited after birth, could not be included. We specifically excluded VLBW adolescent who showed structural abnormalities and major visual or motor dysfunction after birth. More important than the selection of high performing VLBW adolescents was the care taking that

the comparison group of TB adolescents were matched on what we consider to be the two main predictors for functional outcome, socioeconomic status and intelligence. This selection had the advantage that our inferences on potential differences in neural activity can be attributed to early events in otherwise clinically normal adolescents. A potential disadvantage is that by recruiting „best friends“ we were not able to match for age at assessment. The one-year difference between VLBW and TB controls could, however, not explain the differences in brain activity, since tool related activity did not correlate with age and statistical control of age did not change the results. Animal category related activity, however, was negatively correlated with age (data not shown). So larger activity in older VLBW adolescents would rather suggest that VLBW adolescents have a predicted age below the controls. Furthermore, one might argue that older VLBW adolescents may have had worse medical care due to technical improvements and knowledge about outcome. In our case the age range was small and may only have limited or no influence on the findings.

Conclusion

Taken together, we found that very low birth weight premature birth is associated with morphological alterations in the early visual cortex and lateral temporal cortex. These cortical alterations are related to neural specialization within visual semantic category related neural networks, particularly in the dorsal visual stream. Reduced tool related activity in the dorsal stream, but not enhanced animal and picture related activity in VLBW adolescents could be related to early visual cortical alterations. We suggest that prematurity with very low birth weight is associated with impaired development of connections between the early visual cortex and ventral section of the dorsal stream. As a consequence, connectivity between the superior temporal lobe and inferior parietal lobe may be disrupted and neural specialization in those areas is impaired.

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Figure 1: category related activity in groups

Animal and tool related activity is overlaid on axial slices of a canonical anatomical image in term born (TB) and very low birth weight (VLBW) born adolescents separately. Category related neural activity is marked in "red-yellow" for tools > animal pictures and "blue-green" for animal > tool pictures.

Figure 2: ROI analysis of category related activity in groups

Visual semantic category related ROIs displayed on axial and coronal slices of a canonical T1 image in red-yellow (tool > animal picture) and blue-green (animal > tool picture). Bar plots show selective responses for animal (*black*) and tool (*grey*) pictures more than scrambled images in these ROIs for VLBW adolescents and term born (TB) adolescents. Animal category related ROIs (*a-f*) and tool category related ROIs (*1-4*) illustrate residual percent signal changes (with standard error of means) after correction for age at scan. All these ROIs show significant effects of category. Significant main effects and interactions are illustrated by an asterisk ($p < .05$).

Figure 3: Relating volumes to brain activity in VLBW adolescents

The scatter plots show tool > animal picture related brain activity in the left inferior parietal cortex (area PFt) of VLBW and term born adolescents ($x = -42$, $y = -33$, $z = 39$). Data are adjusted for age at scan and total brain volume and are regressed on the thickness of the pericalcarine gyrus (*left part*) and surface area of the superior temporal gyrus (*middle part*). Animal > tool picture related activity in the right lingual gyrus is regressed on the surface area of the bank of the superior temporal sulcus (*right part*). The latter two regressions also adjusted for age and total brain volume. Fits of the regression lines are displayed.

Figure 4: Relating birth weight to brain volumes in VLBW adolescents

The scatter plots show data for the cortical thickness of the pericalcarine gyrus (*left*) and surface area of the superior temporal gyrus (*right*). Data are adjusted for age at scan and total brain volume and are regressed on birth weight of VLBW adolescents. Fits of the regression lines are displayed. The results show significant fits for the relation between birth weight activity and the morphometric measures, which are negative for the cortical thickness of the pericalcarine gyrus, and positive for the surface area of the superior temporal gyrus.

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Highlights

- Visual semantic category related networks are atypical in premature born adolescents with very low birth weight
- Very low birth weight predicts cortical thickness in the primary visual cortex
- Cortical thickness in the primary visual cortex predicts neural specialization for tool related activity in the parietal cortex

Table

Table 1

Demographic and neurocognitive test results for VLBW and TB control adolescents

Group		VLBW				TB				
		n	mean (SD)	median	range	n	mean (SD)	median	range	*p*-value
Demographic	age at scan	11	14.8 (0.2)	15	13.8 - 15.4	11	13.3 (0.2)	13.3	12.1 - 14.1	.000*
	socioeconomic status	11	8.4 (0.5)	8	7 - 12	11	7.3 (0.7)	7	4 - 11	.217*
Intelligence	Estimated total IQ	11	104.8 (2.8)	101	97 - 124	11	108.5 (2.7)	110	94 - 120	.365*
Vision, Motor skills	visual acuity	11	1.2 (0.2)	1.4	0.2 - 2	11	1.7 (0.1)	1.9	0.5 - 2	.023*
	VOT ranked	11	56.8 (11.0)	56.5	0 - 100	11	60.2 (8.8)	68.8	6.2 - 100	0.838
	LPS7	11	51.4 (8.1)	50	40-65	11	62.3 (9.0)	65	45-70	.01*
	Beery - Visual processing	11	97.4 (2.3)	98	82 - 107	11	106.6 (1.9)	106	100 - 118	0.508
	Beery - Visuomotor Integration	11	98.9 (3.5)	98	86 - 124	11	101.1 (2.0)	102	91 -114	0.177
	Beery - Motor Coordination	11	95.6 (2.7)	97	77 - 106	11	105.6 (2.5)	106	94 - 122	0.954
	ZNA - pure motor	11	0.9 (0.4)	0.5	-0.7 - 4.6	11	1.5 (0.4)	1.5	-1.8 - 3.5	.088*
	ZNA - adaptive fine motor	11	-1.4 (0.4)	-1.3	-3.4 - 1.1	11	-0.2 (0.4)	-0.3	-2.2 - 2	0.044

Group		VLBW				TB			
		n	mean (SD)	median	range	n	mean (SD)	median	range	*p*-value
	ZNA - adaptive gross motor	11	-1.8 (0.8)	-1.3	-7.9 - 0.9	11	-1.1 (0.5)	-0.4	-4.9 - 0.7	.606*
	ZNA - static balance	11	0.1 (0.2)	0.1	-0.9 - 1.1	11	0.1 (0.2)	0.1	-1.3 - 1	0.281
naming (% misses)	animal pictures	8	7.5 (2.7)	7.5	5 - 13	11	6.1 (5.2)	5	0 - 15	0.514
	tool pictures	8	15.3 (13.0)	10	3 - 40	11	22.1 (14.5)	22.5	0 - 50	0.312
familiarity rating	animal pictures	8	4.8 (1.6)	4.7	2.6 - 7.3	11	5.0 (1.8)	5.6	1.5 - 7.1	0.788
	tool pictures	8	5.5 (1.7)	5.9	2.9 - 7.2	11	4.9 (1.9)	5.2	2.0 - 7.8	0.519

Note. Mean and standard deviation, median and range for each variable are shown for the group of VLBW and term born adolescents. Group comparisons on variables that did not show normal distributions, were tested using Mann-Whitney U tests (marked with *). Multivariate analysis of variance was used to test group differences for variables with a normal distribution. The latter comparisons were controlled for age at test. Abbreviations: Zurich Neuromotor Assessment (ZNA), Beery-Buktenica (standard score) (Beery), Visual organization task (VOT).

Table

Table 2

Region of interest analysis for VLBW and term born control adolescents

Effect		Anatomical region	Prob. area	MNI coordinates			*p*-value	
				x	y	z		
Category	Occipital	Right posterior fusiform g.	hOC4v	27	-66	-12	0.001	T>A
	Ventral temporal	Left cerebellum /fusiform g.		-24	-48	-21	0.012	T>A
	Ventral temporal	Right fusiform g.		30	-45	-12	0.001	T>A
	Lateral temporal	Right inferior temporal g.		54	-54	-15	0.039	T>A
	Lateral temporal	Left inferior temporal g.		-48	-66	-9	<.001	T>A
	Parietal	Left inferior parietal lobule	IPC (PFt)	-42	-33	39	<.001	T>A
	Parietal	Left inferior parietal lobule	BA 2	-39	-42	54	0.001	T>A
	Parietal	Left superior parietal lobule		-21	-69	42	0.006	T>A
	Parietal	Right superior parietal lobule	SPL (7A)	27	-69	60	0.025	T>A
	Occipital	Left middle occipital g.	BA 18	-45	-84	9	0	A>T
	Occipital	Right cuneus	BA 17	9	-90	18	0	A>T

Effect		Anatomical region	Prob. area	MNI coordinates			*p*-value	
				x	y	z		
	Occipital	Left cuneus		-3	-90	30	0.008	A>T
	Occipital	Right ant. lingual g.	BA 18	12	-63	-3	0.011	A>T
	Occipital	Left cuneus		-12	-96	27	0.001	A>T
	Occipital	Left middle occipital g.	BA 18	-15	-102	9	0.002	A>T
	Occipital	Left middle occipital g.*	hOC3v	-18	-90	-9	0.01	A>T
	Occipital	Right middle occipital g.	hOC5	51	-78	3	0	A>T
	Occipital	Right middle temporal g.*	hOC5	39	-66	12	0.001	A>T
	Occipital	Right inferior occipital g.	hOC4v	39	-81	-12	0.001	A>T
	Occipital	Right lingual g.	hOC3v	24	-87	-15	0.001	A>T
	Occipital	Right calcarine g.*	BA 17	15	-105	0	0.026	A>T
	Ventral temporal	Right fusiform g.		39	-48	-21	0	A>T
	Frontal	Right precentral g.	BA 6	42	-3	45	0.012	A>T
	Frontal	Left middle frontal g.		-42	51	0	0.021	A>T
Group	Occipital	Right lingual g.	hOC3v	24	-87	-15	0.007	VLBW>TB
	Occipital	Left cuneus		-3	-90	30	0.047	VLBW>TB
	Occipital	Left middle occipital g.	BA 18	-45	-84	9	0.044	VLBW>TB
	Frontal	Left middle frontal g.		-42	51	0	0.025	VLBW>TB

Effect		Anatomical region	Prob. area	MNI coordinates x	y	z	*p*-value
Category by group	Parietal	Left inferior parietal lobule	IPC (PFt)	-42	-33	39	0.033
	Occipital	Left middle occipital g.*	hOC3v	-18	-90	-9	0.023
	Occipital	Right lingual g.	hOC3v	24	-87	-15	0.007

Note. Regions are listed showing differential brain activity to viewing pictures of animals and tools. Abbreviations: Animal pictures (A), tool pictures (T), very low birth weight born (VLBW), term born (TB). Group comparisons and interactions between category and group were corrected for age at scan. Local maxima are listed for anatomical regions (AAL) or their nearest region (marked with an asterisk). Probability map classifications were made for Brodmann area 17/18, human occipital cortical areas 3 and 4 and parietal cortex.

Table

Table 3

Structural MRI results for VLBW and TB control adolescents

Group	Region	VLBW	TB	
		mean (SD)	mean (SD)	*p*-value
Cortical thickness (mm)	Parietal cortex	2.52 (0.06)	2.60 (0.08)	0.027
	Occipital cortex	2.08 (0.12)	2.03 (0.12)	0.341 [a]
	Ventral temporal cortex	2.60 (0.16)	2.56 (0.14)	0.707
	Lateral temporal cortex	2.65 (0.10)	2.58 (0.10)	0.333
Cortical area (cm^2)	Parietal cortex	463.92 (39.76)	496.03 (36.04)	0.62
	Occipital cortex	244.74 (22.95)	241.42 (23.11)	0.577 [a]
	Ventral temporal cortex	93.27 (7.53)	102.31 (6.89)	0.023 [a]
	Lateral temporal cortex	231.31 (27.76)	245.61 (25.66)	0.704
Other structures (cm^3)	Total brain volume	1185.04 (111.76)	1245.50 (84.38)	0.728 [b]

Note. Mean and standard deviation (in brackets) is shown for the group of VLBW and term born adolescents. Group comparisons on variables that did not show normal distributions, were tested using Mann-Whitney U tests (marked with [a]). Multivariate analysis of variance was

used to test group differences. These comparisons were controlled for total brain volume and age at scan, except for the total brain volume that was corrected for age at scan only (marked with [b]).

Table

Table 4

Regression of semantic category related activity on brain morphometry in VLBW and term born control adolescents

		VLBW			TB			VLBW vs. TB
		R^2	β	*p*-value	R^2	β	*p*-value	*p*-value
Left inferior parietal lobule, area PFt (MNI: *x* = -42, *y* = -33, *z* = 39)								
Model 1		0.629		0.019	0.302		0.237	
	Total brain volume		-0.908	0.008		-0.551	0.101	0.389
	Age at scan		-0.735	0.021		-0.016	0.959	0.916
Model 2								
Cortical thickness	Parietal cortex	0.055	-0.236	0.308	0.012	-0.144	0.733	0.587
	Occipital cortex	0.189	-0.449	0.031	0.049	-0.343	0.489	0.213
	Ventral temporal cortex	0.006	-0.093	0.742	0.085	0.332	0.358	0.324
	Lateral temporal cortex	0.014	0.129	0.612	0.007	-0.09	0.793	0.544
Cortical area	Parietal cortex	0.165	1.614	0.05	0.022	0.256	0.651	0.209
	Occipital cortex	0.056	-0.319	0.3	0.000	0.003	0.995	0.406
	Ventral temporal cortex	0.000	0.021	0.954	0.034	0.304	0.569	0.685

		VLBW			TB			VLBW vs. TB
		R^2	β	*p*-value	R^2	β	*p*-value	*p*-value
	Lateral temporal cortex	0.265	1.207	0.004	0.114	0.604	0.280	0.103
Animal > Tool related activity in right lingual gyrus (MNI: x = 24, y = -87, z = -15)								
Model 1		0.246		0.322	0.314		0.221	
	Total brain volume		-0.548	0.175		-0.216	0.486	0.568
	Age at scan		-0.496	0.215		-0.544	0.102	0.764
Model 2								
Cortical thickness	Parietal cortex	0.243	0.498	0.111	0.053	-0.296	0.471	0.063
	Occipital cortex	0.108	0.339	0.316	0.041	0.313	0.525	0.767
	Ventral temporal cortex	0.016	0.151	0.706	0.049	-0.253	0.486	0.397
	Lateral temporal cortex	0.053	-0.247	0.049	0.336	-0.595	0.036	0.234
Cortical area	Parietal cortex	0.024	0.615	0.646	0.237	0.847	0.096	0.322
	Occipital cortex	0.114	-0.455	0.300	0.107	0.49	0.293	0.097
	Ventral temporal cortex	0.041	0.307	0.547	0.012	0.18	0.735	0.835
	Lateral temporal cortex	0.003	-0.132	0.868	0.509	1.277	0.003	0.006

Note. Multiple regression analysis explaining tool and animal picture related brain activity in VLBW born adolescents and term born controls. Brain activity was tested only for the ROIs that showed significant group differences in category related activity. The left middle occipital gyrus was not listed because there were no significant results. In a first step total brain volume and age at scan entered the regression model (M1). Then in a second step brain morphometry (cortical thickness, surface area) of visual cortical areas entered the model (M2). Explained additional variance for each model (R^2), significance level (p-value) and standardized coefficients (β) for each region and group are summarized. Positive correlations mean that higher values on structural measures are associated with larger category related activity. The results show that thickness of the occipital cortex and surface area of the lateral temporal cortex are associated with larger tool related activity in VLBW adolescents. Surface area of the lateral temporal cortex was associated with animal related activity in term born adolescents.

Table 5

Predictions of visual brain morphometry by birth weight and gestation age in VLBW adolescents

		M1		M2		Birth weight		Gestation age	
		R^2	*p*-value	R^2	*p*-value	β	*p*-value	β	*p*-value
Cortical thickness	Parietal cortex	0.021	0.918	0.210	0.484	-0.162	0.689	0.471	0.273
	Occipital cortex	0.064	0.766	0.566	0.061	-0.712	0.037	0.388	0.202
	Ventral temporal cortex	0.292	0.251	0.022	0.910	0.144	0.706	0.071	0.855
	Lateral temporal cortex	0.134	0.563	0.076	0.758	0.213	0.605	-0.21	0.616
Cortical area	Parietal cortex	0.937	0.000	0.017	0.401	0.098	0.342	-0.1	0.344
	Occipital cortex	0.447	0.093	0.100	0.551	-0.332	0.305	0.074	0.814
	Ventral temporal cortex	0.567	0.035	0.033	0.788	-0.1	0.734	0.170	0.567
	Lateral temporal cortex	0.818	0.001	0.110	0.061	0.342	0.027	-0.1	0.424
Other brain region volumes	Total brain volume*	0.304	0.079	0.151	0.426	0.234	0.442	0.292	0.338

Note. Multiple regression analysis in VLBW born adolescents explaining brain morphometry in the visual system (cortical thickness and surface area). In a first step total brain volume and age at scan entered the regression model (M1), then in a second step birth weight and gestation age entered the model (M2). Explained additional variance for each model (R^2) and significance level (p-value) are listed for each model. In addition standardized coefficients (β) for birth weight and gestation age are summarized. Total brain volume was separately predicted by age at scan (M1), birth weight and gestation age (M2). The results show that the second model predicted cortical thickness of the occipital cortex and surface area of the lateral temporal cortex, which were largely explained by birthweight.

Figure